

The COVID generation: the neurodevelopmental consequences of in-utero COVID-19 exposure

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ABSTRACT

Background: In historical viral epidemics, such as the H1N1 influenza and Zika viruses, prenatal exposures were correlated with risk for neuropsychiatric conditions in offspring. However, the long-term effects of prenatal COVID-19 viral exposure on offspring neurodevelopment are still being discovered.

Methods: We prospectively recruited mother-baby dyads during the COVID-19 pandemic, who had been exposed to the SARS-CoV-2 virus during pregnancy (2020–2022) into a longitudinal infant brain development study and compared them to a low-risk normative pre-pandemic cohort (2016–2019). Quantitative 3-D volumetric magnetic resonance imaging (qMRI) was conducted at a neonatal visit when the infant was approximately 2 weeks of corrected age. Behavioral development was assessed using the Bayley Scales of Infant and Toddler Developmental, Third Edition (BSID-III) and the Infant-Toddler Social and Emotional Assessment (ITSEA), when the child was approximately 2 years old. An ordinary least squares regression model was used to determine the neurodevelopment of toddlers relative to their exposure to the SARS-CoV-2 virus. Mediation analyses were performed to assess how in utero exposure to SARS-CoV-2 affected the newborn brain and toddler developmental outcomes. Analyses were adjusted for maternal age and educational level, infant sex, and total brain volume on qMRI.

Findings: This study prospectively recruited 142 mother baby dyads, 103 from a normative prepandemic cohort and 39 pairs who had been exposed to the SARS-CoV-2 virus during pregnancy. In utero viral exposure was associated with altered newborn regional brain volumes in the cortical gray matter ($q = 0.001$), subcortical gray matter ($q < 0.001$), cerebral white matter ($q = 0.005$), and left hippocampus ($q = 0.008$). Viral exposure additionally was associated with lower cognition ($q = 0.010$) and social emotional ($q = 0.001$) scores on the BSID-III and higher scores on the internalizing domain ($q = 0.040$) of the ITSEA. The lower cognition scores on the BSID-III following SARS-CoV-2 exposure were mediated in part by the altered cortical gray matter volumes (21.9 % mediated, $p = 0.034$). These lower cognition scores further mediated the relationship between the SARS-CoV-2 viral exposure and increased internalizing behavior scores on the ITSEA (61.0 % mediated, $p = 0.040$).

Conclusions: This study reports that in utero SARS-CoV-2 viral exposure was associated with decreased cognitive skills in toddlers at age 2, and this association was mediated by cortical gray matter volumes in the newborn brain. In addition, toddler cognitive scores further mediated an increase in toddler internalizing behaviors. These findings highlight the need for ongoing assessments for children born during the COVID-era.

1. Introduction

As of December 2023, when the Centers for Disease Control and Prevention halted data collection regarding the SARS-CoV-2 virus,

nearly 3.5 million babies had been born in the United States since the discovery of the novel SARS-CoV-2 virus and COVID-19 pandemic (Maternal and Infant Characteristics, 2024). Of those, 163,140 infants were exposed to SARS-CoV-2 in utero as a result of their mothers' viral

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infection (Maternal and Infant Characteristics, 2024). Though direct vertical transmission of the SARS-CoV-2 virus from mother to fetus is rare (Kotlyar et al., 2021; Flaherman et al., 2020; Dumitriu et al., 2021; Woodworth et al., 2020), the indirect consequences of such prenatal exposures remain to be fully elucidated. To date, there are conflicting reports regarding early neurobehavior for young children born to mothers with prenatal SARS-CoV-2 infection (Favre et al., 2024; Hill et al., 2024; Veloso et al., 2024; Jaswa et al., 2024; Thomason et al.). These studies have utilized the Ages and Stages Questionnaire to assess 12-month-old infants and varied between reporting no significant difference following viral exposure (Favre et al., 2024; Jaswa et al., 2024) and reporting significant developmental risk (Hill et al., 2024). Some of these discrepancies may stem from assessments that rely solely on parental report and the potential vulnerability of parental bias, as well as age ranges assessed that may not fully capture evolving developmental domains. Additional explanations for the discrepancies may be due to nuances in maternal viral infection, both in the timing of exposure to the virus and in the severity of the illness for the mother. A recent study by Shook et al. did note increased risk of adverse outcomes in toddlers of age following third trimester viral exposure, though the potential mechanisms leading to these findings remain unclear (Shook et al., 2025).

The ongoing and emerging longer-term consequences of viral exposure are still relatively unknown for women and their offspring. This study seeks to better define the neurodevelopmental consequences of in utero COVID-19 viral exposure by first delineating the changes seen on quantitative measures of newborn brain development following COVID-19 exposure, as well as reporting on developmental and behavioral differences found at 2 years of age, using a combination of parent-reported and practitioner-assessed metrics.

2. Methods

2.1. Study participants

Mother-baby dyads in the DC metro area were prospectively recruited in a longitudinal observational study, including neonatal MRI and toddler-age developmental assessments (Lu et al., 2022). Dyads were recruited during the pandemic from July 2020 through December 2022 and compared with a healthy normative cohort recruited from 2016 to 2019. Information regarding SARS-CoV-2 infection, including timing of the illness, severity of symptoms, and any pertinent vaccinations were collected both by self-report and from medical records. Exclusion criteria included multiple gestation pregnancy, known or suspected congenital infection not including the SARS-CoV-2 virus, documented chromosomal abnormalities, or any maternal contraindication to MRI. Additionally, subjects reporting the use of medications or substances other than prenatal vitamins or supplements were excluded (e.g., prescription medicine, tobacco, marijuana, or alcohol). SARS-CoV-2 exposures were determined through serial self-reported surveys of the COVID-19 in Pregnancy and Early Childhood (COPE) (Carlsson et al., 2021) as well as medical records, including laboratory testing for SARS-CoV-2.

2.2. Maternal psychological distress

Maternal psychological distress was additionally evaluated in each cohort to account for any additional stressors during the pandemic that may have compounded the effect of viral exposure on the developing fetus. The Spielberger State-Trait Inventory assesses both 'state' anxiety, which measures the anxiety at the time of taking the test, and 'trait' anxiety, which measures a more chronic personality trait of anxiety. Scores of above 40 on either test are considered indicative of a clinically high state of anxiety (Caci et al., 2003). The Perceived Stress Scale was used to assess the level of stress the mother was experiencing, with scores above 15 indicating clinically elevated stress (Cohen et al., 1983).

Women were evaluated at the newborn visit at the same time the infants underwent MRI scanning. Women who tested above threshold on at least one of the assessments were considered to have notable psychological distress.

2.3. MRI data acquisition

MRI studies were performed on neonates on a 3 T MR Scanner (Discovery MR750; GE Healthcare) and an 8-channel high resolution brain array receiver-only head coil (T2-weighted, 3-dimensional [3D] CUBE sequence; repetition time, 2500 ms; echo time, 64.7 ms; flip angle, 90°; $0.625 \times 0.625 \times 1 \text{ mm}^3$). The acquisition time was 3 to 4 min. Infants were scanned during natural sleep after being fed, swaddled in warm blankets, and immobilized with a vacuum pillow to prevent the need for sedation.

2.4. Image processing

A quality assessment of each scan was conducted before analysis, and 3D brain images with severe motion artifacts that affected the ability to distinguish brain tissues such as the cortical gray matter, white matter, and cerebellum were excluded from analysis. The regions of interest, namely the cortical gray matter, subcortical gray matter, cerebral white matter, left and right hippocampus, left and right amygdala, and the cerebellum, were determined based on prior reports (Lu et al., 2022; Weiner et al., 2024; Wu et al., 2022). Regions were automatically segmented using 3D U-Net (Zhao et al., 2022) and manually corrected using open-source ITK-SNAP software using the coronal, sagittal, and axial views. A representative image of the MRI scans and segmentation performed is shown in Fig. 1.

2.5. Toddler developmental assessments

Measures of toddler neurodevelopmental status were performed by licensed pediatric developmental psychologists (M.L. and C.M) blinded to clinical findings. Neurodevelopmental assessments were conducted using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), when the child was approximately 2 years of age (Carter and Briggs-Gowan, 2006).

The BSID-III is comprises of a practitioner evaluated component as well as a parent survey (Bayley, 2012). The practitioner evaluated component measures of development across domains of cognition, language, and motor skills. The BSID-III parent reported survey assesses social-emotional skill development (Bayley, 2012). Composite scores on each of these domains lower than 85 are considered at risk of deficit or delay (Bayley, 2012). Any child whose scores indicated a delay on at least one domain of the BSID-III was categorized as overall 'at risk.'

The Infant-Toddler Social and Emotional Assessment (ITSEA) is a parent-assessed measure that evaluates child social emotional development (Carter and Briggs-Gowan, 2006). The ITSEA is comprised of 4 domains: externalizing (activity/impulsivity, aggression/defiance, and peer aggression), internalizing (depression/withdrawal, general anxiety, separation distress, and inhibition to novelty), dysregulation (negative emotionality, sleep, eating, and sensory sensitivity), and competence (compliance, attention, mastery, motivation, imitation/play, empathy, and prosocial peer relations) (Carter and Briggs-Gowan, 2006). Externalizing, internalizing, dysregulation scores of 65 or higher and competence domain scores of 35 or lower indicate a deficit or delay (Carter and Briggs-Gowan, 2006). Any child whose scores indicated a delay on at least one ITSEA domain was categorized as overall 'at risk.'

2.6. Statistics

Multivariable regression models based on ordinary least squares were used to evaluate the association between (1) in-utero SARS-CoV-2 exposure and infant neurodevelopment, (2) viral exposure and

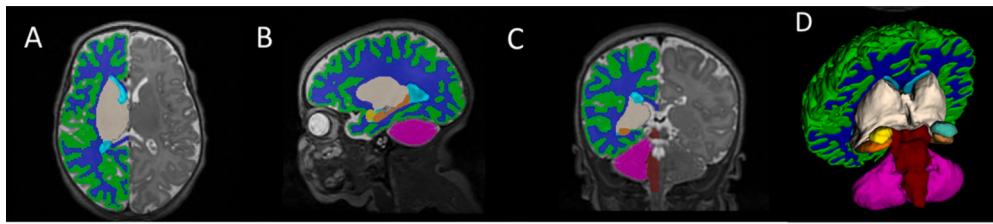


Fig. 1. Representative image of newborn brain MRI scan and segmentation in the axial (A), sagittal (B), and coronal planes (C), with resulting 3D segmentation (D). Segmented regions of interest are color-coded as: cortical gray matter (green), cerebral white matter (blue), subcortical gray matter (grey), left amygdala (cyan), right amygdala (yellow), left hippocampus (brown), right hippocampus (orange), cerebellum (fuchsia).

neurodevelopment, (3) brain structure and neurodevelopment, and (4) viral exposure and brain structure. Covariates of maternal age and education, infant sex, and total brain volume on qMRI were included. Multivariable logistic regression model was used to explore the association between the COVID-19 pandemic and the composite development risk. A causal mediation analysis was utilized to evaluate whether newborn brain volumes mediate the association between in utero exposure to SARS-CoV-2 and subsequent neurodevelopment (path diagram shown in Fig. 2). The direct effect, c , is the pathway from X to Y with the mediator controlled. The mediation effect is the product of a and b which is represented by the pathway from X to Y through the mediator. Finally, the total effect is the sum of the direct and mediation effects. The primary hypothesis of interest in a mediation analysis is to see whether the effect of SARS-CoV-2 on infant development can be mediated by a change in regional brain volumes. The secondary hypothesis is that the change in cognitive scores on the BSID-III resulting from SARS-CoV-2 exposure mediates a change in social-emotional development on the ITSEA.

Where more than two comparisons were performed, multiplicity was adjusted with Benjamini-Hochberg method based on the number of outcomes when multiple correlated brain regional volumes were considered as the outcome variables. Where appropriate, adjusted p -values were labeled as q -values to differentiate them from the raw p -values. Statistical significance was considered at the 0.05 level for 2-sided tests. All analyses were performed using R Statistical Software® version 4.3.1 (R Core Team 2023).

3. Results

3.1. Study participants

This study prospectively enrolled 207 mother-infant dyads. One hundred three (103) were recruited from a prepandemic normative healthy cohort (March 1, 2014, to December 31, 2019), and 104 were recruited during the COVID-19 pandemic (June 1, 2020, to June 30, 2022). In the pandemic cohort, 39 mothers had confirmed exposure to

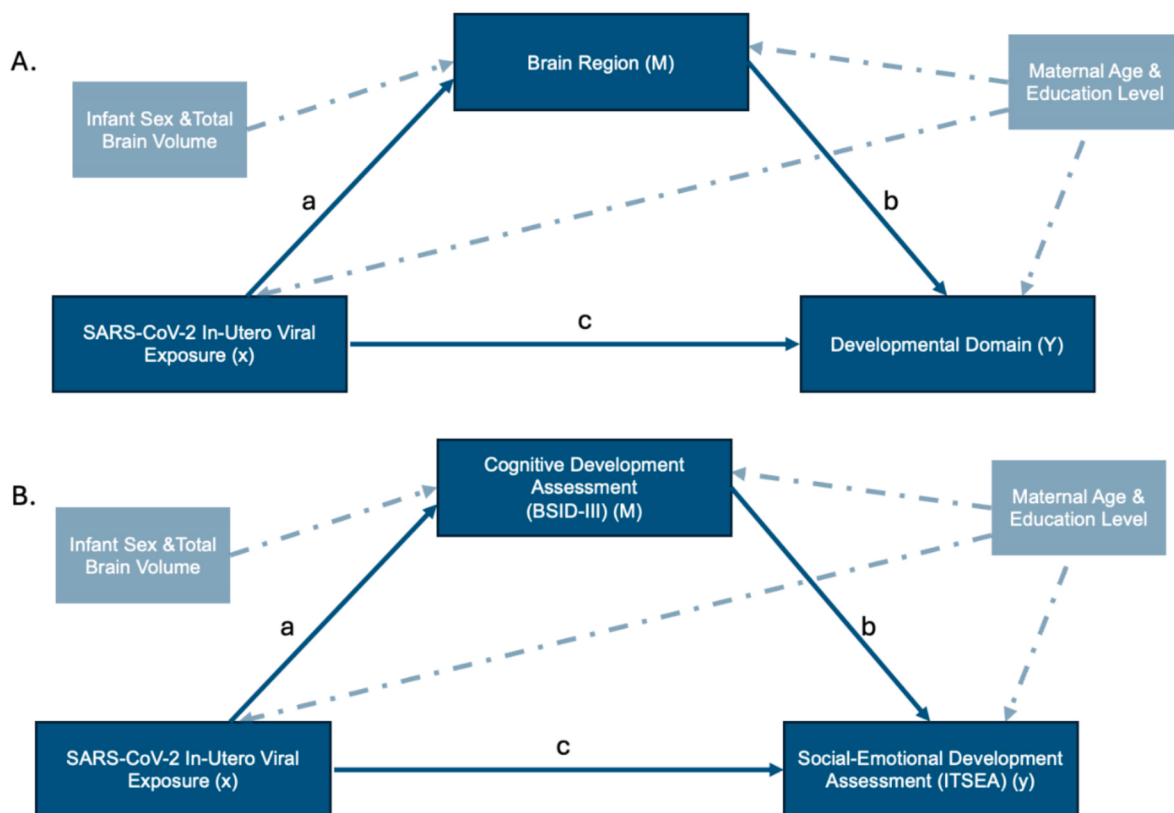


Fig. 2. Mediation analysis path diagram. Moderator model is $M = a * X$ and Outcome model is $Y = b * M + c * X$, with both models controlled for sex, maternal age, maternal education, and gestational age at MRI. Indirect effect = $a * b$, Direct effect = c , Total effect = $a * b + c$, Proportion mediated = $a * b / (a * b + c)$. A. Mediation model assessing how regional brain volumes mediate the relationship between SARS-CoV-2 exposure and subsequent behavioral outcomes. B. Mediation model assessing how cognitive scores on the BSID-III as a result of SARS-CoV-2 viral exposure affects subsequent social-emotional development on the ITSEA.

SARS-CoV-2 during pregnancy and were included in this analysis. None of the women with SARS-CoV-2 infection had been previously vaccinated against the virus. Of the remaining 142 remaining mother-infant dyads, none were removed from the study due to MRI image quality or brain injury detected on scan. One hundred thirty-six (136/142, 96 %) had completed BSID-III Assessments, 103 from the prepandemic cohort (100 %) and 33 (85 %) from the exposed cohort. Additionally, 108/142 (76 %) had complete ITSEA assessments; 73 in the prepandemic cohort (70 %) and 35 (90 %) in the viral-exposed cohort. Table 1 summarizes participant demographic characteristics. There was no statistically significant difference in reported psychological distress between cohorts: 21.7 % of the mothers in the prepandemic cohort were experiencing psychological distress at the time of the newborn MRI, compared with 29.4 % of the mothers from the exposed cohort ($p = 0.31$). The infants in the SARS-CoV-2 exposed cohort had statistically significant lower gestational age at birth (39.2 (38.1–40.4) weeks) compared with the prepandemic cohort (39.6 (38.3–40.4) weeks) ($p = 0.03$), though this difference was unlikely to have significant clinical implications.

3.2. Association between SARS-CoV-2 exposure and newborn regional brain volumes

Infants exposed to the SARS-CoV-2 virus in utero showed significantly larger cortical gray matter volumes ($\beta = -8096.40$, 95 % CI: -11179.55 , -5013.25 , $q < 0.001$) and left hippocampal volumes ($\beta = -62.73$, 95 % CI: -108.85 , -16.60 , $q = 0.008$) than infants who were not exposed to the virus (Fig. 3). By contrast, infants exposed to the virus had significantly smaller subcortical gray matter volumes ($\beta = 1299.84$, 95 % CI: 601.90 , 1997.85 , $q < 0.001$) and white matter volumes ($\beta =$

6259.79 , 95 % CI: 2825.55 , 9694.03 , $q = 0.005$) than infants who were not exposed (Fig. 3). No other brain region was significantly associated with SARS-CoV-2 exposure.

3.3. Association between SARS-CoV-2 exposure and toddler developmental outcomes

Overall, 14 % of toddlers in the pre-pandemic group were at high risk for developmental delays on the BSID-III compared with 51.6 % in the SARS-CoV-2 exposed group ($p < 0.01$; Table 1), unadjusted for covariates. On the ITSEA, 11 % of children in the pre-pandemic cohort were at high risk for behavioral problems compared with 24.7 % in the SARS-CoV-2 exposed group ($p = 0.05$; Table 1), unadjusted for covariates.

Toddlers exposed to SARS-CoV-2 in utero showed significantly lower composite cognitive scores on the BSID-III than those who were not exposed ($\beta = 9.05$, 95 % CI: 2.68 , 15.42 , $q = 0.010$; Fig. 4A). SARS-CoV-2 exposed toddlers similarly showed lower composite scores on the social-emotional scale of the BSID-III than unexposed toddlers ($\beta = 20.85$, 95 % CI: 9.75 , 31.95 , $q = 0.001$; Fig. 4B). While there was no significant association between SARS-CoV-2 exposure and overall composite language score on the BSID-III ($\beta = 2.98$, 95 % CI: -3.80 , 9.77 , $q = 0.30$, Fig. 4C), receptive language scores significantly decreased following in-utero exposure to the virus ($\beta = 1.55$, 95 % CI: 0.11 , 2.99 , $p = 0.034$, Fig. 5B).

There was a significant relationship between SARS-CoV-2 exposure and scores on the internalizing domain of the ITSEA ($\beta = -5.82$, 95 % CI: -10.32 , -1.33 , $q = 0.04$; Fig. 5). There was no other significant association between the viral exposure and the ITSEA externalizing, dysregulation or competence domains (Fig. 6).

Table 1
Study Population.

N (%) or Median [IQR] Number of Subjects	All Subjects <i>N</i> = 142	Prepandemic <i>N</i> = 103	SARS-CoV-2 Exposed <i>N</i> = 39	<i>p</i>	<i>N</i> *
Neonatal Sex				0.60	142
Male	67 (47.2 %)	50 (48.5 %)	17 (43.6 %)		
Female	75 (52.8 %)	54 (51.5 %)	22 (56.4 %)		
Gestational Age at Birth (weeks)	39.4 [38.3–40.3]	39.6 [38.3–40.4]	39.2 [38.1–40.4]	0.03	142
Birth Weight (grams)	3270 [3015–3609]	3300 [3007–3655]	3235 [3066–3431]	0.35	140
Gestational Age at MRI (weeks)	42.1 [40.7–43.9]	41.9 [40.4–43.0]	44.4 [42.9–46.2]	<0.01	142
Maternal Age (year)	34.0 [31.0–36.8]	34.5 [31.0–38.0]	33.0 [28.0–35.5]	0.05	142
Maternal Distress				0.31	117
Low	89 (76.1 %)	65 (78.3 %)	24 (70.5 %)		
High	28 (23.9 %)	18 (21.7 %)	10 (29.4 %)		
Maternal Ethnicity				0.14	135
Hispanic	25 (15.5 %)	16 (15.8 %)	9 (26 %)		
Nonhispanic	110 (81.5 %)	85 (84.2 %)	25 (73.5 %)		
Maternal Education*:				0.94	132
High School	12 (9.09 %)	6 (6.00 %)	6 (18.3 %)		
College	41 (21.1 %)	40 (40.0 %)	1 (3.03 %)		
Pregnancy Complications				0.29	142
Preeclampsia	8 (5.63 %)	6 (5.83 %)	2 (5.13 %)		
Gestational Diabetes	2 (1.41 %)	0 (0.00 %)	2 (5.13 %)		
Graduate School	79 (59.8 %)	54 (54.0 %)	26 (78.8 %)		
ITSEA Risk*:				0.05	138
Low	91 (64.1 %)	65 (89.0 %)	26 (74.3 %)		
High	51 (35.9 %)	8 (11.0 %)	9 (24.7 %)		
BSID-III Risk*:				<0.01	136
Low	104 (76.5 %)	88 (85.4 %)	16 (48.4 %)		
High	32 (30.8 %)	15 (14.0 %)	17 (51.6 %)		

*N** denotes the number of subjects in the analysis.

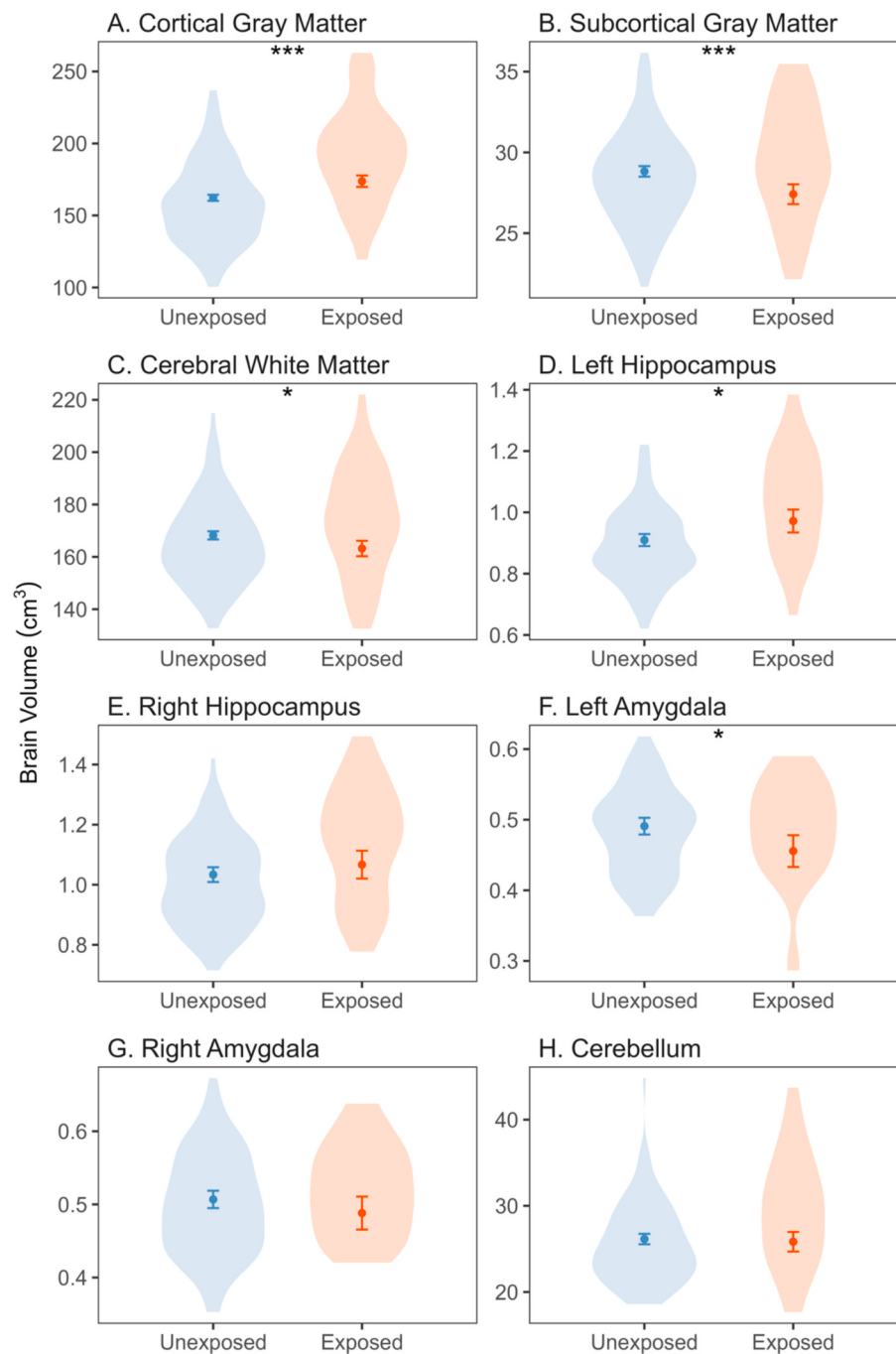


Fig. 3. Association between COVID-19 Exposure and Newborn Brain Volumes. A. Cortical Gray Matter B. Subcortical Gray Matter C. Cerebral White Matter. D. Left Hippocampus E. Right Hippocampus F. Left Amygdala G. Right Amygdala H. Cerebellum. Data is shown as adjusted means $\pm$ standard error. *** $q < 0.001$ ** $q < 0.01$.

3.4. Regional brain volumes mediate the effect of SARS-CoV-2 exposure on developmental outcomes

A mediation analysis was performed to further characterize the relationship between SARS-CoV-2 in utero viral exposure, newborn regional brain volumes, and toddler developmental outcomes. We can report that 21.9 % of the relationship between in utero SARS-CoV-2 viral exposure and lower cognition scores on the BSID-III was mediated by the volume of the cortical gray matter (Mediation Effect = -0.23, 95 % CI: -0.054 to -0.01, $p = 0.034$; Table 2). The newborn cortical gray matter volumes mediated 62.4 % of the relationship between in utero SARS-CoV-2 exposure and scores on the language assessment domain of the

BSID-III (Mediation Effect = -0.35, 95 % CI: -0.70 to -0.11, $p < 0.001$; Table 2). Additionally, cerebral white matter volumes were found to mediate 31.4 % of the relationship between SARS-CoV-2 exposure and motor scores on the BSID-III (Mediation Effect = -0.18, 95 % CI: 0.45, 0.00, $p = 0.048$; Table 2).

Left hippocampal volumes were found to mediate 29.0 % of the relationship between SARS-CoV-2 exposure and overall risk on the ITSEA (Mediation Effect = 0.09, 95 % CI: -0.45, 0.00, $p = 0.014$), meaning the risk of the child scoring at risk on one or more of the ITSEA domains.

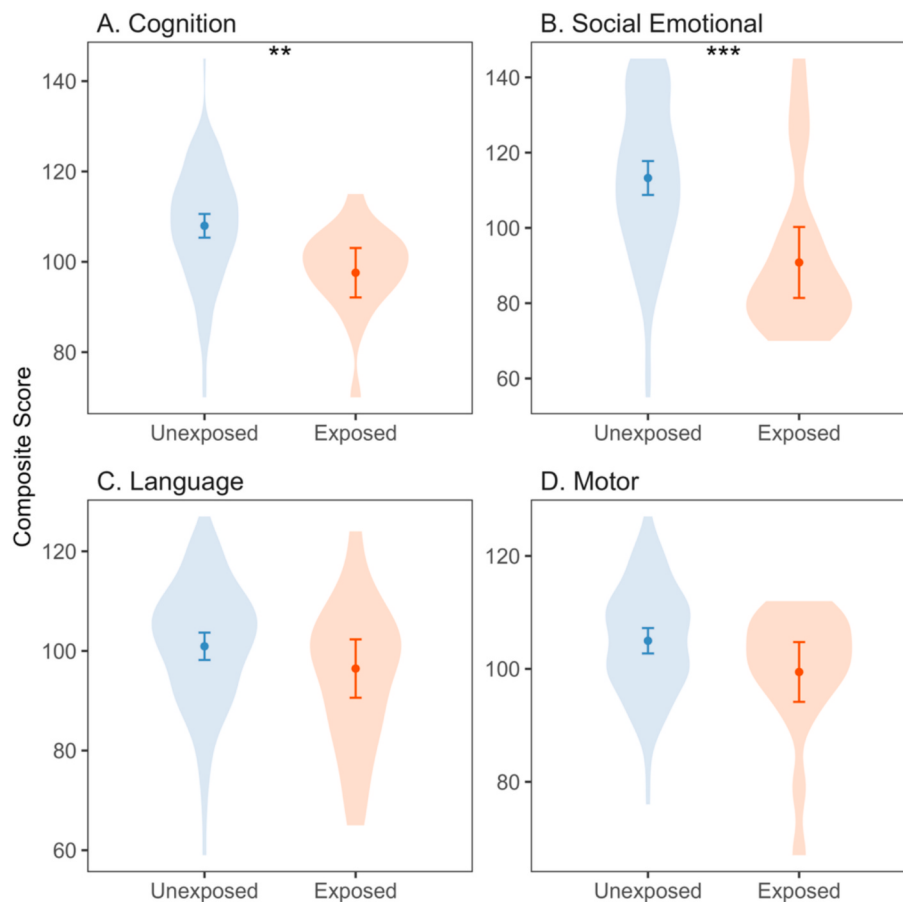


Fig. 4. Association between COVID-19 Exposure and Toddler Development on the BSID-III. A. Cognition B. Social Emotional C. Language D. Motor. Data is shown as adjusted means $\pm$ standard error. * $q < 0.05$ ** $q < 0.01$.

3.5. Cognitive abilities mediate the effect of SARS-CoV-2 on behavioral outcomes

High cognitive scores on the BSID-III were significantly associated with lower risk scores on the internalizing domain of the ITSEA ($\beta = -0.24$, 95 % CI: -0.41 , -0.08 , $q = 0.01$; Table 3). There was no other significant association between cognitive abilities and other ITSEA outcomes.

A mediation analysis was performed to further characterize the relationship between SARS-CoV-2 exposure, toddler cognitive abilities, and internalizing behaviors. Twenty percent (20 %) of the effect of COVID-19 exposure on internalizing behaviors on the ITSEA was mediated by the cognitive abilities of the toddler (Mediation Effect = -2.49 , 95 % CI: -4.88 to -0.10 , $p = 0.040$).

4. Discussion

This study reports that in utero SARS-CoV-2 viral exposure results in decreased cognitive skills in toddlers mediated by structural differences in the regions of the newborn brain. Just over 50 % of the children in the SARS-CoV-2-exposed cohort scored “at risk” of developmental delay on the BSID-III, compared with only 14 % in the healthy pre-pandemic cohort, highlighting the potential impact of these exposures on this generation of children. Finally, toddler cognitive scores mediated the association between in utero SARS-CoV-2 exposure and toddler internalizing behaviors.

While direct vertical transmission of the SARS-CoV-2 virus from mother to fetus has been shown to be rare (Kotlyar et al., 2021; Yates and Mulkey, 2024), indirect effects of maternal infection may impact the developing fetus through several potential mechanisms (Hill et al.,

2024; Kocher et al., 2023; Shook et al., 2024). Mothers who had contracted SARS-CoV-2 during pregnancy showed elevated serum IL-6 and IL-17A levels at birth, (Hill et al., 2024) where these two particular cytokines have been shown to be related in developmental delays as a consequence of maternal immune activation (Wong and Hoeffler, 2018; Zhang et al., 2024). In addition to immune system activation, exposure to the virus may alter DNA methylation and downstream genomic pathways. Infants exposed to SARS-CoV-2 in utero have been reported to experience epigenetic changes in DNA methylation in genes related to autism spectrum disorder, such as *ABHD16A*, *PGAP3*, and *ALDH3A2* (Hill et al., 2024), which could result in significant changes in gene expression. The mechanism of action underlying these methylation changes and subsequent neurodevelopmental outcomes, has not yet been fully outlined, and further studies involving neuronal cell lines, postmortem brain tissue or animal models are necessary to fully explore these biologic mechanisms.

SARS-CoV-2 infection has additionally been linked with placental dysfunction and hypoxia (Indra et al., 2024). Evidence of placental changes in the setting of maternal SARS-CoV-2 infection in pregnancy, including severe chronic histiocytic intervillitis, massive perivillous fibrin deposition, and inflammation around trophoblasts (Indra et al., 2024), are correlated with intrauterine fetal growth restriction (Abdulghani et al., 2017) and further linked to neurodevelopmental risk in infants (Andescavage et al., 2023).

This study builds upon an earlier report of altered regional neonatal brain volumes after in utero SARS-CoV-2 exposure by relating volumetric measures of brain growth with toddler cognition, language, motor, and social-emotional development. (Andescavage et al., 2024) To better understand this phenomenon, this work now demonstrates that deficits in cognition and language development were mediated by

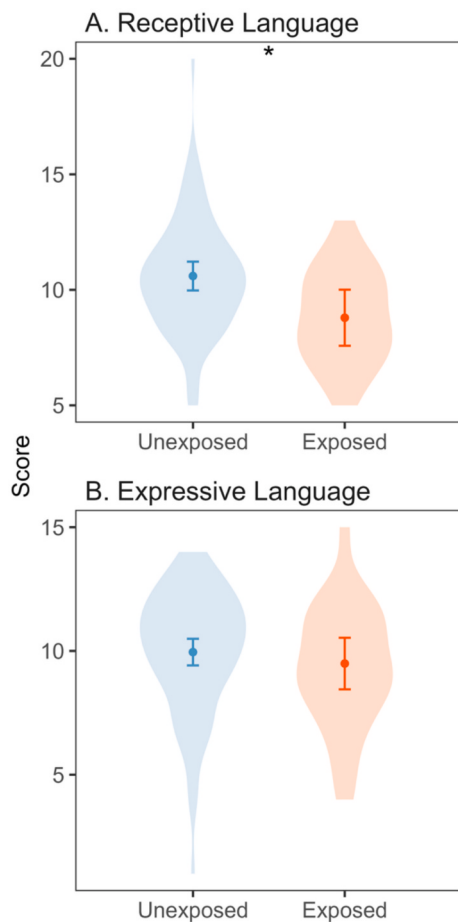


Fig. 5. Association between COVID-19 Exposure and Receptive and Expressive Language Skills on the BSID-III. A. Receptive Language. B. Expressive Language. Data is shown as adjusted means $\pm$ standard error. * $q < 0.05$.

increased cortical gray matter volumes at the newborn stage. Enlarged cortical gray matter volumes in early childhood have been linked with subsequent neurobehavioral outcomes, including autism (Courchesne et al., 2003; Lucibello et al., 2019). This initial overgrowth recedes in early childhood to match neurotypical peers, but is suspected to contribute to cognitive differences in children with autism (Courchesne et al., 2003).

We also report that the effect of prenatal SARS-CoV-2 exposure is associated with internalizing behaviors in toddlers. These behaviors, which include symptoms of depression and anxiety in toddlers, are independent risk factors for the subsequent development of mood disorders as the child ages. These associations were significantly mediated by the toddlers' cognitive scores and prenatal viral exposure. This connection previously has been established in young adults, with anxiety diagnoses in young adults correlating with cognitive deficits (Castaneda et al., 2008; Ruthmann et al., 2023). Our results, which examine this connection at a much earlier age, suggest that early cognitive deficits may influence anxiety symptoms as the child develops.

Though this work sought to determine the effects of prenatal viral exposure on offspring outcomes, broader implications from the COVID-19 pandemic may have exerted specific effects on fetal programming and early childhood. In particular, elevated levels of maternal psychological symptoms of stress and anxiety as a result of the pandemic resulted in decreased white matter, hippocampal, and cerebellar volumes in the fetus (Lu et al., 2022) and lower left amygdalar volumes in the newborn (Weiner et al., 2024). Additionally, DNA methylation changes also have been reported in children born during the pandemic in genes related to stress process such as *NR3C1* (Kocher et al., 2023)

regardless of SARS-CoV-2 exposure; which suggests that multiple exposures may converge to influence neurodevelopment. Despite the known associations between the COVID-19 pandemic with increases in maternal stress and anxiety (Ahmad and Vismara, 2021; Barbosa-Leiker et al., 2021) the cohorts in this work did not reflect significant differences in postnatal maternal distress. Further work is required to see how children exposed to the virus potentially differ from their peers who grew up with similar societal and lifestyle constraints, and if these early differences persist or diminish over time.

4.1. Limitations

It is important to note the limitations of our study. First, as highlighted above, it is necessary to acknowledge that the COVID-19 pandemic brought about many changes beyond direct viral exposure. Though there were no significant differences in postnatal psychological distress between groups, prenatal mental health data were limited. Similarly, there may have been additional non-viral pandemic related exposures independent of maternal psychological distress that influenced our findings. Second, while this study included the greater Washington DC region and was open to pregnant women of all races, ethnicities, and resources, the population included was relatively homogenous, with overall high levels of education and little variability in the racial make-up. Therefore, this study may not necessarily be representative of other communities or regions. This study was also limited by the relatively small sample size of our SARS-CoV-2 exposed cohort, though strengthened by the well-characterized measures of brain structure and early development. The smaller cohort also limited our ability to fully differentiate potential effects based on the timing of exposure and the severity of illness. Prior work by our group on this cohort reported no significant difference in the newborn brain structures resulting from either of these factors (Andescavage et al., 2024), but a larger cohort may show variations in developmental outcomes relative to exposure timing and severity, and aid in the generalizability and reliability of this data.

5. Conclusions

Children exposed to the SARS-CoV-2 virus in utero display lower cognitive abilities than children who had not been exposed, mediated in part by the neonatal cortical gray matter volumes. Cognitive ability in toddlers also mediated the association between in utero SARS-CoV-2 exposure and their early social-emotional development. These findings highlight the need for continued surveillance to best identify and provide early interventions for at-risk children and provide new insights regarding prenatal exposures on early fetal programming. Further studies into the longitudinal effects of this exposure are currently ongoing.

6. Access to data statement

Dr. Andescavage had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Data is available upon request to Dr. Andescavage at nnifor@childrensnational.org.

7. Role of funder/sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CRedit authorship contribution statement

Susan Weiner: Writing – original draft, Investigation, Formal

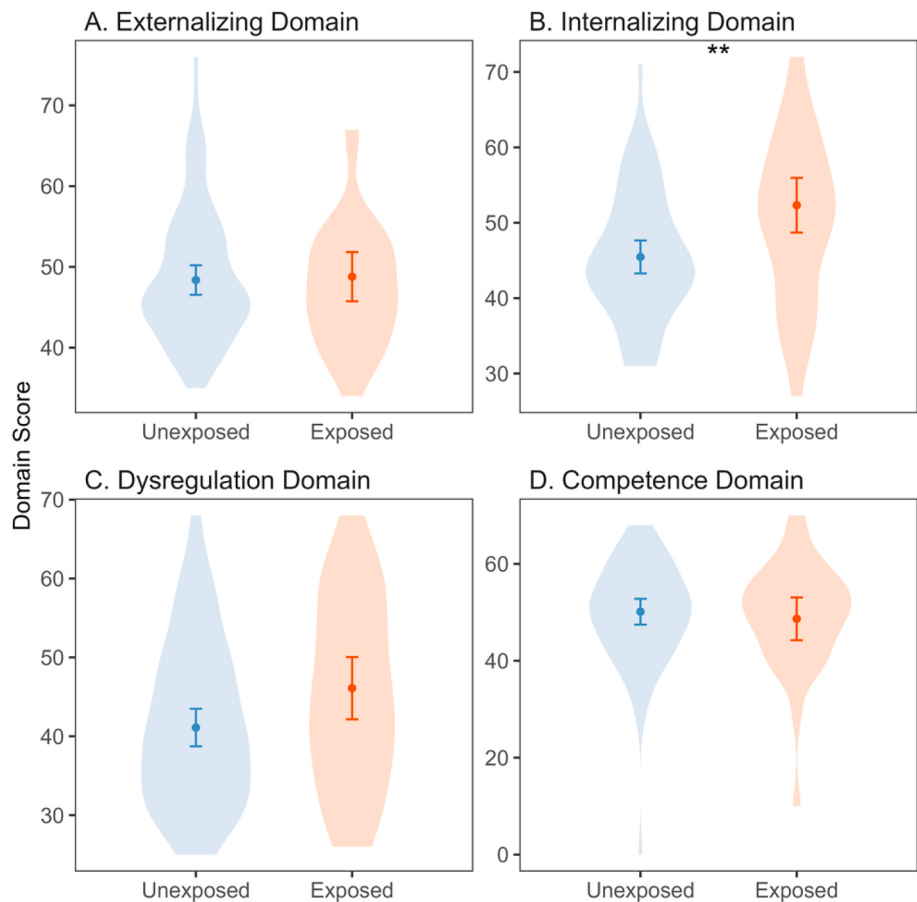


Fig. 6. Association between COVID-19 Exposure and Behavioral Assessment on the ITSEA. A. Externalizing Domain B. Internalizing Domain C. Dysregulation Domain D. Competence Domain. Data is shown as adjusted means $\pm$ standard error. *** $q < 0.01$.

Table 2
Mediation effect of newborn regional brain volumes on the relationship between in Utero SARS-CoV-2 exposure and toddler developmental outcomes.

SARS-CoV-2 exposure (X)	Brain region (M)	Developmental assessment	Mediation effect (standardized β)	95 % CI	p	% Mediated
Viral Exposure	Cortical Gray Matter	BSID-III Cognition	-0.23	(-0.54, -0.01)	0.034	21.9 %
		BSID-III Language	-0.35	(-0.70, -0.11)	<0.001	62.4 %
Viral Exposure	Cerebral White Matter	BSID-III Motor	-0.18	(-0.45, 0.00)	0.048	31.4 %
Viral Exposure	Left Hippocampus	ITSEA Overall Risk	0.09	(0.01, 0.20)	0.014	29.0 %

Table 3
Association between toddler cognitive scores on the BSID-III and performance on toddler social-emotional assessment on the ITSEA.

BSID-III domain	ITSEA domain	Beta value	q -Value
Cognition	Externalizing	0.018	0.82
Cognition	Internalizing	-0.245	0.01*
Cognition	Dysregulation	-0.029	0.82
Cognition	Competence	0.124	0.45

* $q < 0.05$, Adjusted for maternal age and education.

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Data availability

Data will be made available on request.

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